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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,803	05/22/2001	Jeffrey J. Rade	71699/55591	8907

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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,803	RADE ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 September 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8-11 and 14-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8-11 and 14-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/8/03 has been entered.

Upon the entry of the RCE, the amendments of claims 1, 3, 4, 6, 8, 9, and 24 have been entered. Claims 7 and 12 have been canceled. Claims 1, 3-6, 8-11, 14-28 are pending and under current examination.

Claim Objections

Claim 1 is objected to because "APC" in step c should be spell out the first time it appears in the claims.

Claims 3 and 6 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 3 and 6 are drawn to a method of transplantation, which depend from claim 1, drawn to a method for treating a vascular graft of a mammal. The preamble of the claims (treating a graft) does not agree with the method steps (transplantation). Accordingly, claims 3 and 6 fail to further limit the subject matter of the base claim. Applicant is required to cancel

the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 4 recites that the graft is transplanted into the mammal before performing step a) of the method of claim 1. However, as such, step (a) of the method could not be performed ex vivo as required by claim 1. Accordingly, claim 4 fails to further limit the subject matter of the base claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 5 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claim 5 recites that the method of claim 1 is performed on the vascular graft in vivo, whereas claim 1 recites that step (a) of the method is performed ex vivo. Accordingly, claim 5 fails to further limit the subject matter of the base claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 8 is objected to because an article should precede "protein c" in line 1.

Claims 26 and 27 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 26 and 27 recite "wherein the graft is an artificial graft", whereas the base claim 24 recites that the graft is from a mammal, thus, the graft would be autologous, but not artificial. Accordingly, claims 26 and 27 fail to further limit the subject matter of the base

claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-6, 8-11, 14-28 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims are vague and indefinite because of the claim recitation, "functional fragment thereof". This is because the lower limit of the fragment and the type of the function is not specified, and thus the metes and bounds of the claims are unclear.

Claims 1 and 24 are vague and indefinite because the amended claims recite, "early graft failure". The specification fails to define the term, it is unclear what period in length is considered as "early graft", and thus, the metes and bounds of the claims could not be readily determined.

Claims 1 and 24 are vague and indefinite because the amended claims recite the phrase, "provided...". It is unclear whether the phrase defines the agents encoded by the nucleic acid as recited in step (a), or as a condition that APC would increase as recited in step (c), thus, the metes and bounds of the claim is uncertain. For the sake of a compact prosecution, the phrase has been interpreted as defining the nucleic acids of step (a) for the prior art purpose.

Claims 1 and 24 are vague and indefinite because the claims recite the phrase, "and step a) of the method...". It is unclear whether the phrase further limits step a), or as a condition that APC would increase, thus, the metes and bounds of the claim is uncertain. In view of the prosecution history, the phrase has been interpreted as further limiting step a). Appropriate clarification is required.

Claims 1 and 24 recite the limitation "the APC". There is insufficient antecedent basis for this limitation in the claim.

Claim 1 is vague and indefinite because of the claim recitation in step c), "increasing the APC sufficient to treat the graft". It is unclear where the APC is located (e.g. graft) and whether increasing the APC is the consequence of expressing the agent(s), or another step in addition to expressing the agent in the cells. If it represents an additional step, then what is the means for increasing the APC and how to treat the graft. Thus, the metes and bounds of the claims are unclear.

Claim 8 recites the limitation "the level of protein C activation". There is insufficient antecedent basis for this limitation in the claim.

Claim 9 recites the limitation "the increased protein C level". There is insufficient antecedent basis for this limitation in the claim.

Claim 21 recites the limitation "the host". There is insufficient antecedent basis for this limitation in the claim.

Claim 24 is vague and indefinite because it is unclear whether increasing the APC in step c is the consequence of expressing the agent(s), or another step in addition

to expressing the agent in the cells. If it represents an additional step, then what is the means for increasing the APC. Thus, the metes and bounds of the claims are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

WRITTEN DESCRIPTION REQUIREMENT

Claims 1, 3-6, 8-11, 14-28 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in papers #6, 9, 11 and following.

In the 9/8/03 response, applicants argue in addition to reiterate the arguments of paper #8, that EPCR has been mentioned more than one time in the specification. In response, the Office action refers to the one time was in the context of the particular section in page 7 as pointed by the applicants, not discussing the entire specification. Nevertheless, it has been indicated repeatedly that merely reciting "EPCR" multiple times does not provide adequate written description for the "functional fragments" of the EPCR or TM or NF-kB inhibitor. What is required is a teaching of either the enumeration of the species encompassed by the genus, or the structure-functional relationship of the recited molecule, such as a consensus region that is critical for the function of EPCR or TM or NF-kB inhibitor, that would allow the modification of the molecule. The court states, "IN CHEMICAL CASE WHERE APPLICANT DISCLOSES THAT ONE SPECIES OF A CLASS OF CHEMICALS WILL ACCOMPLISH CERTAIN PURPOSE WITHOUT NAMING ANY OTHERS OF CLASS TO WHICH IT BELONGS OR WITHOUT SO DESCRIBING THE SPECIES AND ITS MODE OF OPERATION AS TO CALL ATTENTION TO FACT THAT OTHER MEMBERS OF CLASS ARE ITS EQUIVALENTS AND WILL PERFORM

SAME FUNCTIONS, HE IS NOT ENTITILED TO BROADER SCOPE OF DISCLOSED INVENTION BY CLAIMING WHOLE GROUP EVEN THOUGH THOSE SKILLED IN ART MAY KNOW THAT IN SOME RESPECTS AT LEAST DIFFERENT MEMBERS OF GROUP ARE EQUIVALENTS; CERTAIN MEMBERS OF WELL-DEFINED GROUP OF CHEMICALS MAY BE EQUIVALENTS FOR ONE PURPOSE AND NOT EQUIVALENT FOR ANOTHER. (*In re Soll*, 97 F.2d623, 38 USPQ 189 (CCPA 1938) emphasis added). In the instant case, the specification fails to teach genuses of functional fragments for EPCR and NF-KB inhibitor (IKB) or TM, and which fragment qualifies as functional, and thus, the specification fails to provide an adequate description for what is now claimed.

Applicants then indicated that it is not clear why the Revised Interim Guidelines were cited.

In response, it is cited because applicants' disclosure fails to meet the requirement set forth in the guideline, that the specification fails to adequately describe what is an essential or critical element in the claimed method, and which is not conventional in the art, and to indicate the standard for determining whether the written description was met, i.e. when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus, and in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus.

Applicants go on to argue that they have cited numerous references showing the fragments of TM.

Although several publications concerning TM are cited in the specification or could be found in the relevant art, the functional effect of the mutation or modification to the TM was determined on a case-by-case basis, the prior art of record do not teach the

functional fragments (e.g. the cited U.S. '207 patent) or a consensus region that is critical for the genus; and claims encompass more than functional fragments of the TM. The specification fails to provide adequate description for genus of functional fragments of TM, EPCR, and IKB.

Therefore, for reasons of record and those set forth above, the rejection stands.

ENABLEMENT REQUIREMENT

Claims 1, 3-6, 8-11, 14-28 stand rejected under 35 U.S.C. 112, first paragraph, for reasons of record advanced in papers #6, 9, 11 and following.

Applicants first argue that the position of protein chemistry is one of the most unpredictable field in biology contradicts the rejection under §103. In response, the obviousness rejection does not rely on a reference using the functional fragments of the TM, EPCR, or IKB, thus, there is no contradiction between the two rejections.

Applicants then argue that the cited references are old and outdated. In response, the art has not significantly changed since the publication of *Bowie et al,* and *Rudinger et al.* For example, *Skolnick et al* (TIBTECH 2000 Jan;18:34-9) teach, "SEQUENCE-BASED METHODS FOR FUNCTION PREDICTION ARE INADEQUATE BECAUSE OF THE MULTIFUNCTIONAL NATURE OF PROTEINS. HOWEVER, JUST KNOWING THE STRUCTURE OF THE PROTEIN IS ALSO INSUFFICIENT FOR PREDICTION OF MULTIPLE FUNCTIONAL SITES" (abstract). They further teach, "KNOWING A PROTEIN'S THREE-DIMENSIONAL STRUCTURE IS INSUFFICIENT TO DETERMINE ITS FUNCTION" (box 1, page 35). One cannot predictably extrapolate the teachings of the specification to the scope of the claims because the skilled artisan

cannot envision the detailed structure of polypeptides encompassed by these claims and which fragments can serve as a functional TM, EPCR, or NF-kB inhibitor (IKB). Moreover, it is unclear exactly what modifications and variations can be tolerated in these proteins and still allow proper function. Thus, reciting "functional fragments" numerous times does not provide an enabling disclosure commensurate with the scope of the claims.

With respect to the therapeutic aspect of the enablement rejection, the rejection is withdrawn in view of claim amendment limiting the method to resisting *early* graft failure in *autologous* graft, and because Kim et al publication teaches that TM overexpression restored graft APC-production and reduced local thrombin generation. However, it is noted when the amendment was made to limit the step a of the base claims to an ex vivo cell transfection procedure (amendment submitted 1/21/03), the dependent claims 4 and 5 have not been amended accordingly, therefore, the rejection of claims 4 and 5 still stands for reasons of record as they read on *in vivo* transfection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The prior rejection of claims 1, 3-6, 8-12, 14-22, and 24-27 under 35 U.S.C. 102(e) as being anticipated by *French et al* (US 6,290,949) is withdrawn in view of claim amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-6, 8-11, and 14-28 stand rejected and the rejection has been modified under 35 U.S.C. 103(a) as being unpatentable over *French et al* (US 6,290,949), *Fukudome et al* (US 5,852,171), and in view of *Thomas et al* (Transplant 1999;68:1660-73), *Stephens et al* (J Autoimmun 1997;10:293-8) and *Larson et al* (US 6,309,380).

French et al teach a method for delivering vectors carrying therapeutic agents to cardiovascular cells such as the smooth muscle cell or endothelial cell in a host suffering vascular injury or immunological rejection of transplanted organ and tissues (column 5, lines 24-30), or underwent angioplasty (column 6, line 67), wherein the vector comprises coding sequences for thrombin inhibitors such as TM, and the protein C, etc. (column 5, lines 39-42), wherein the vector could be introduced into the cells of autologous SVG or arteries by in vivo or ex vivo routes (see columns 17-18). *French et al* go on to teach that two or more different therapeutic gene sequences can be

provided (column 16, lines 44-67), the transgene expression could last for weeks, and the vector could be used in combination with conventional drugs, such as anti-thrombin factors (column 17, lines 15-30). *French et al* also teach expression cassette having a promoter (column 12, lines 15-17) and replication defective Adv (column 14, lines 43-44). *French et al* do not teach combining the EPCR or IKB in the TM multi-gene therapy regimen nor the particular conventional anti-coagulant, coumadin.

Fukudome et al teach that EPCR and TM share the same function in activating endothelial cell protein C, and both are down regulated during an inflammatory response such as exposure to TNF (e.g. abstract). *Fukudome et al* teach cloning and sequencing EPCR, and using such for modulating inflammation (e.g. column 8, § II). They particularly teach that the function of EPCR could be enhanced by overexpressing the EPCR in endothelium to coat vascular grafts in patients with vascular disease or on stents in cardiac patients (column 9, lines 31-34). *Fukudome et al* do not clearly teach supplementing TM with EPCR. However, *French et al* have suggested administering multiple agents in TM therapy, and *Fukudome et al* do teach that both TM and EPCR decreased during inflammation pointing to the necessity for supplementing both agents.

Thomas et al teach administering a NF-kB inhibitor (DSG) together with an anti-CD3 immunotoxin to suppress the inflammatory response to mismatched renal graft, and observed enhanced graft survival. *Thomas et al* also teach pre-treating the graft with the IKB. *Thomas et al* do not teach administering a nucleic acid encoding the IKB, however, *French et al* and *Fukudome et al* have taught so.

Stephens et al teach that cells (NIT-1) expressing IKB were protected from killing by auto-reactive T cells *in vivo*, illustrated the feasibility of using expressed IKB.

Larson et al teach conventional anti-coagulants known in the art, such as coumadin (see paragraph bridging columns 1 & 2), illustrated that it is known in the art to use coumadin as an anti-coagulant.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ EPCR along with TM in the combination gene therapy as taught by *French et al* and as suggested by *Fukudome et al*. It would have also been obvious to combine the conventional anti-coagulant agents with the expression vectors as taught by French et al, and select one of the conventional anti-coagulant drugs such as coumadin as taught by *Larson et al* or IKB as taught by Thomas et al and Stephen et al with a reasonable expectation of success. It would also have been obvious to one of ordinary skill in the art at the time the invention was made to present the recited agents as a kit in a commercial process for the convenience and profit of the commercial activity. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday,

except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is **703-308-0196**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QL
February 23, 2004